^{18}F-FDG-Directed Surgery and ^{18}F-FDG-Directed Interventional Procedures

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Contents

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Portions of the contents of this chapter are adapted from 5 prior Open Access articles:
1. Povoski et al.: A comprehensive overview of radioguided surgery using gamma detection probe technology. *World Journal of Surgical Oncology*, 2009, **7:**11.; doi:10.1186/1477-7819-7-11; http://www.wjso.com/

K. Herrmann et al. (eds.), *Radioguided Surgery: Current Applications and Innovative Directions in Clinical Practice*, DOI 10.1007/978-3-319-26051-8_25

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2. Povoski et al.: Multimodal imaging and detection approach to ^{18}F-FDG-directed surgery for patients with known or suspected malignancies: a comprehensive description of the specific methodology utilized in a single-institution cumulative retrospective experience. *World Journal of Surgical Oncology*, 2011, **9:**152.; doi:10.1186/1477-7819-9-152; http://www.wjso.com/content/pdf/1477-7819-9-152.pdf; © 2011 Povoski et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/2.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
3. Povoski et al.: ^{18}F-FDG PET/CT oncologic imaging at extended injection-to-scan acquisition time intervals derived from a single institution ^{18}F-FDG-directed surgery experience: feasibility and quantification of ^{18}F-FDG accumulation within ^{18}F-FDG-avid lesions and background tissues. *BMC Cancer* 2014 **14:**453.; doi:10.1186/1471-2407-14-453; http://www.biomedcentral.com/content/pdf/1471-2407-14-453.pdf; © 2014 Povoski et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
4. Chapman et al.: Comparison of two threshold detection criteria methodologies for determination of probe positivity for intraoperative in situ identification of presumed abnormal ^{18}F-FDG avid tissue sites during radioguided oncologic surgery. *BMC Cancer.* 2014 **14:**667.; doi:10.1186/1471-2407-14-667; http://www.biomedcentral.com/content/pdf/1471-2407-14-667.pdf; © 2014 Chapman et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.
5. Povoski et al.: Feasibility of a multimodal ^{18}F-FDG-directed lymph node surgical excisional biopsy approach for appropriate diagnostic tissue sampling in patients with suspected lymphoma. *BMC Cancer* 2015 **15:**378.; doi: 10.1186/s12885-015-1381-z; http://www.biomedcentral.com/content/pdf/s12885-015-1381-z.pdf; © 2015 Povoski et al; licensee BioMed Central Ltd. This is an Open Access article distributed under the terms of the Creative Commons Attribution License (http://creativecommons.org/licenses/by/4.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

Abstract

The use of positron-emitting and high-energy gamma photon-emitting radiopharmaceuticals, like fluorine-18 fluorodeoxyglucose (^{18}F-FDG), for real-time cancer detection and surgical guidance within the operating room and for real-time guidance of diagnostic and therapeutic interventional procedures within the interventional radiology suite, has great clinical potential. This technology may allow for (1) real-time intraoperative staging of the extent of disease; (2) real-time intraoperative surgical planning and execution of the necessary and most appropriate operation, determination of the extent of surgical resection, and determination of the completeness of surgical resection; (3) real-time pathologic evaluation of intact surgical resected specimens for the confirmation of completeness of surgical resection and for surgical margin assessment; (4) real-time pathologic evaluation of diagnostically biopsied tissues for confirmation of correctness of tissue diagnosis; and (5) real-time guidance of diagnostic and therapeutic interventional procedures within the interventional radiology suite. This chapter discusses (1) the history and development of positron imaging and detection, (2) the fundamental basis for the use of ^{18}F-FDG in positron imaging and detection strategies, (3) the inherent limitations of ^{18}F-FDG in positron imaging and detection strategies, (4) radiation detection devices utilized during ^{18}F-FDG-directed surgery, (5) the clinical

applications of real-time ^{18}F-FDG-directed surgery and real-time ^{18}F-FDG-directed interventional procedures, (6) timing issues related to ^{18}F-FDG-directed surgery, (7) the inherent challenge of in situ detection of ^{18}F-FDG with a gamma photon detection device, and (8) occupational radiation exposure during ^{18}F-FDG radioguided surgical procedures.

25.1 The History of the Development of Positron Imaging and Detection

The theoretical physics framework behind the implementation of positron imaging and detection is the basic concept of electron-positron annihilation [1–6], which was first realized in the 1930s. Within any given biological system, electron-positron annihilation results when a positron (i.e., a positively charged antimatter counterpart of an electron), emitted from the nucleus of a radionuclide and travels only a few millimeters, collides with an electron (i.e., a negative charged particle) within a biological tissue and generates two resultant high-energy 511 keV gamma photons traveling in opposite directions.

The development of clinical applications of positron imaging and detection has its origins in the early 1950s [7, 8] and occurred far before the subsequent availability of fluorine-18 fluorodeoxyglucose (^{18}F-FDG) in the late 1970s [9, 10]. The first reported clinical application of positron imaging technology in humans was published by Gordon L. Brownell and William H. Sweet at the Massachusetts General Hospital (Boston, Massachusetts, USA) in 1953 and consisted of the collection of three-dimensional data using a prototype positron imaging device on patients with brain tumors who were intravenously injected with arsenic-74 [7, 8]. Subsequent technologic advancements over the ensuing two decades culminated in the development of the first commercially available positron emission tomography (PET) device by the early 1970s for generating whole-body positron transaxial tomographs [7, 11–14], thus representing the antecedent of current-day PET imaging devices.

Currently, positron imaging and detection, in the specific form of ^{18}F-FDG PET imaging, is a well-established cancer imaging modality that is routinely used in the clinical management of a wide variety of solid malignancies [6, 15–25]. ^{18}F-FDG PET is generally combined with "anatomical" imaging, by way of computed tomography (CT), for attempting to maximize the geographic localization and spatial recognition of sites of ^{18}F-FDG avidity to corresponding anatomic structures. A wide range of diagnostic utilities of ^{18}F-FDG PET/CT have been clinically investigated and implemented [6, 15–25]. Those diagnostic clinical applications include (1) initial cancer diagnosis, (2) initial cancer staging, (3) subsequent cancer restaging, (4) therapy planning, (5) monitoring therapy response, (6) surveillance for cancer survivors, and (7) cancer screening for at-risk populations. As a step beyond these diagnostic clinical cancer imaging utilities, there has been emergent interest in the feasibility of utilizing ^{18}F-FDG for real-time cancer detection and surgical guidance within the operating room [6, 26–76] and for real-time guidance of diagnostic and therapeutic interventional procedures within the interventional radiology suite [6, 77–95].

25.2 The Fundamental Basis for the Use of ^{18}F-FDG in Positron Imaging and Detection Strategies

The radionuclide ^{18}F has a relatively short physical half-life of approximately 110 min [6, 96, 97]. The radioactive decay pattern of ^{18}F is predominantly (97 %) by way of positron emission (i.e., beta plus decay emission). The maximum positron radiation emission energy of ^{18}F is approximately 635 keV, giving ^{18}F a relatively low maximum positron radiation emission energy level as compared to other positron-emitting

radionuclides. As a result, the positron emitted from the nucleus of ^{18}F travels only a very short distance (i.e., approximately 1–2 mm) within a biological tissue before interacting/colliding with an electron (i.e., a negative charged particle). This interaction/collision of the emitted positron with the electron and the resultant electron-positron annihilation within a biological tissue generates two resultant high-energy 511 keV gamma photons traveling in opposite directions [1–6, 96, 97]. These resultant high-energy 511 keV gamma photons can travel many, many centimeters within a biological tissue. As based upon the initial positron emission and subsequent electron-positron annihilation process which occurs by ^{18}F, the detection of ^{18}F within biological tissues can potentially be accomplished by one of two mechanisms: (1) a direct mechanism of detection of positron emissions (i.e., beta plus decay emissions) using a beta plus detection device or (2) an indirect mechanism of detection of the resultant high-energy 511 keV gamma photons arising from electron-positron annihilation process using a gamma photon detection device [6].

Dating back to the work of Otto Heinrich Warburg in the early 1930s from the Kaiser-Wilhelm-Gesellschaft zur Förderung der Wissenschaften (Berlin-Dahlem, Germany), it has long been recognized that malignant tumors have an accelerated rate of glucose metabolism and have an increased rate of glucose transport and glucose utilization [6, 98–101]. The biochemical transport and processing mechanisms related to ^{18}F-FDG, a non-physiologic ^{18}F-labeled analog of glucose, within malignant cells are also well described within the scientific literature [6, 102–104]. ^{18}F-FDG within the circulatory system is transported into cells (both malignant cells and normal cells) by a facilitated diffusion mechanism involving specific glucose transporters (i.e., GLUT transporters). Once it is within the cell, ^{18}F-FDG is phosphorylated to ^{18}F-FDG-6-phosphate by the enzyme hexokinase. However, unlike ^{18}F-FDG, ^{18}F-FDG-6-phosphate cannot be readily transported across the cellular membrane of either malignant cells or normal cells, thus essentially entrapping the ^{18}F-FDG-6-phosphate within those cells. The enzyme glucose-6-phosphatase is responsible for dephosphorylating ^{18}F-FDG-6-phosphate back to ^{18}F-FDG within the intracellular environment and is present in relatively lower levels within malignant cells as opposed to normal cells. Additionally, unlike glucose-6-phosphate, ^{18}F-FDG-6-phosphate cannot be utilized as a substrate in the metabolic steps of glycolysis, hence attributing to the further accumulation of ^{18}F-FDG-6-phosphate within those cells. This overall process which results in the intracellular accumulation ^{18}F-FDG-6-phosphate is thought to occur more readily in malignant cells than in normal cells secondary to the combination of the overexpression of the glucose transporters GLUT 1 and GLUT 3 by malignant cells, the higher level of hexokinase within malignant cells, and the lower level of glucose-6-phosphatase within malignant cells, thus leading to proportionally greater accumulation of ^{18}F-FDG-6-phosphate within malignant cells as compared to normal cells. This elegantly elucidated biochemical transport and processing mechanism represents the fundamental basis behind the clinical application of ^{18}F-FDG for the detection of malignant tumor using positron imaging and detection strategies (i.e., diagnostic PET imaging technology and various radiation detection probe technologies) [6, 98–104].

25.3 Inherent Limitations for the Use of ^{18}F-FDG in Positron Imaging and Detection Strategies

Despite the fact that these biochemical transport and processing mechanisms lead to the greater accumulation of the phosphorylated form of ^{18}F-FDG within malignant cells as compared to normal cells, there are several inherent limitations regarding the utilization of ^{18}F-FDG for the detection of malignant tumor using positron imaging and detection strategies [6, 75, 102, 105–107]. First, ^{18}F-FDG can readily accumulate within various normal tissues (i.e., brain, heart, mucosa and smooth muscle of the stomach, small intestines and colon, thyroid, liver, spleen, and

brown fat) which typically have physiologic propensity for ^{18}F-FDG accumulation. Second, ^{18}F-FDG can also readily accumulate within tissues representing benign disease processes (i.e., infection, inflammation, and trauma). The basis for these first two limitations is the fact that ^{18}F-FDG is not a cancer-specific imaging and detection agent. Third, ^{18}F-FDG is excreted by way of the urinary tract (kidneys, ureters, and bladder), thus leading to accumulation within those structures. Fourth, alterations in tissue uptake of ^{18}F-FDG can occur in patients with elevated blood glucose levels/impaired glucose metabolism, in patients receiving insulin, and in obese patients. An accumulation of ^{18}F-FDG within normal tissues leads to intrinsically higher background levels of ^{18}F-FDG activity within normal tissues located in proximity to adjacent sites of elevated ^{18}F-FDG activity representing malignant tumor. This may be particularly challenging when the malignant tumor site itself has a relatively low level of ^{18}F-FDG activity, leading to a relatively low target-to-background ratio (i.e., low tumor-to-background ratio) of the radiation emissions of ^{18}F-FDG.

25.4 Radiation Detection Devices Utilized during ^{18}F-FDG-Directed Surgery: Mechanisms for the Detection of ^{18}F-FDG and Device Specifications

25.4.1 General Considerations

As previously mentioned, there are two mechanisms for how ^{18}F-FDG within biological tissues can be detected by a radiation detection device: (1) the direct detection of positron emissions (i.e., beta plus decay emissions) using a beta plus detection device and (2) the detection of the resultant high-energy 511 keV gamma photons arising from electron-positron annihilation process using a gamma photon detection device [6]. The ability to successfully detect ^{18}F-FDG within a site of suspected malignancy is highly dependent upon the specific type of radiation detection device utilized and its performance parameters [6, 108]. The most important performance parameters for any given radiation detection device are (1) overall sensitivity (i.e., efficiency, detected count rate per unit of activity), (2) spatial selectivity (i.e., radial sensitivity distribution), (3) spatial resolution (i.e., lateral sensitivity distribution), (4) energy resolution (i.e., spectral discrimination), and (5) contrast.

Radiation detection devices are categorized as either scintillation detectors or semiconductor ionization detectors [6, 108]. The basis for how a scintillation-type detection system works is that the radiation emitted from the radionuclide excites atoms within the scintillation crystal, producing visible light in proportion to the energy absorbed, and for which a photomultiplier enhances the resultant visible light and converts it into an electrical pulse which is quantified by a detection unit. Examples of inorganic scintillation materials used in scintillation detectors include thallium-activated sodium iodide (NaI[Tl]), thallium-activated cesium iodide (CsI[Tl]), sodium-activated cesium iodide (CsI[Na]), samarium-activated lutetium orthooxysilicate (LSO), bismuth germanate (BGO), cerium-activated gadolinium orthosilicate (GSO[Ce]), cerium-activated lutetium yttrium orthosilicate (LYSO[Ce]), and cerium-activated lutetium gadolinium oxyorthosilicate (LGSO[Ce]). Examples of organic ("plastic") scintillation materials used in scintillation detectors include anthracene ($C_{14}H_{10}$), stilbene ($C_{14}H_{12}$), and naphthalene ($C_{10}H_8$). The basis for how a semiconductor ionization-type detection system works is that the radiation emitted from the radionuclide produces free electrons as it passes through and ionizes the semiconductor crystal, creating an electrical pulse which is quantified by a detection unit. Examples of crystalline materials used in semiconductor ionization detectors include cadmium telluride (CdTe), cadmium zinc telluride (CdZnTe), mercuric iodide (HgI_2), and silicon.

There are advantageous and disadvantageous features to both the scintillation-type detection system design and the semiconductor ionization-type detection system design [6, 108]. On one

hand, scintillation-type detection systems have higher sensitivity (especially for medium-energy to high-energy gamma photons) but have poorer energy resolution and scatter rejection. Likewise, scintillation-type detection probes tend to have a much bulkier and heavier probe head profile. On the other hand, semiconductor ionization-type detection systems have higher-energy resolution and scatter rejection but have lower sensitivity (especially for medium-energy to high-energy gamma photons). Likewise, semiconductor ionization-type detection probes tend to have a much more compact and light-weight probe head profile.

25.4.2 Gamma Photon Detection

The detector component of a gamma detection probe generally consists of an inorganic scintillator detector or a semiconductor ionization detector [6, 108]. Most commercially available handheld gamma detection probes are generally designed for detecting radioisotopes of gamma-ray energies in the low-energy emission (0–150 keV) range and medium-energy emission (150–400 keV) range, thus allowing successful detection of radioisotopes such as technetium-99 m (^{99m}Tc; 140 keV and 142 keV), indium-111 (^{111}In; 171 keV and 247 keV), iodine-123 (^{123}I; 159 keV), and iodine-125 (^{125}I; 35 keV) [6, 76, 108]. However, most commercially available handheld gamma detection probes are not specifically designed for detecting resultant high-energy 511 keV gamma emissions emanating from the electron-positron annihilation process that is characteristic of high-energy gamma photon-emitting radionuclides, like ^{18}F. As a result, there has been a recent appearance of commercially available handheld gamma detection probes that are specifically intended for attempting to detect high-energy 511 keV gamma emissions, and for which these high-energy gamma detection probes have been designated as "PET" probes. The overall weight and physical dimensions of any such "PET" probe is generally a function of the thickness of side and back shielding (with materials like lead, tungsten, gold, or platinum) and the length of collimation (i.e., extension of shielding in a forward direction beyond the distal face of the detector in the direction of the radiation source being counted) that is thought to be necessary to block adjacent background radiation, to limit the field-of-view, and to collimate the head of the probe, with the intention of limiting the area of tissue contributing to the probe count rate and of providing better spatial resolution between areas of tissue of differing radioactivity levels [6, 73, 108, 109]. All conventional attempts to improve upon the current "PET" probe design by further increasing the degree of side/back shielding or the collimation length to further block adjacent background radiation, or by increasing crystal diameter/thickness to capture a greater percentage of 511 keV gamma emissions, are generally counterproductive, as such conventional approaches will simply result in a "PET" probe configuration that is prohibitively too large in physical size, too heavy in weight, and potentially of significant greater cost. Alternatively, in order to attempt to bypass these physical barriers related to the degree of side and back shielding, collimation, and crystal diameter/thickness in designing handheld gamma detection probes specifically intended for the detection of 511 KeV gamma emissions, efforts have been redirected toward engineering more novel "PET" probe designs for which their efficacy is not dependent upon side and back shielding, collimation, or crystal diameter/thickness. Several examples of alternative design concepts for "PET" probe include secondary K-alpha x-ray fluorescence [73, 76, 109], active electronic collimation [39, 61, 64, 66, 70, 76, 110–112], and other crystal geometry designs using multiple small crystals with specific novel geometric configurations [76, 113, 114] for optimizing and maximizing background rejection capabilities. These innovative alternative design concepts for improving the efficacy of detection of high-energy gamma photon-emitting/positron-emitting radionuclides, some of which have already been successfully applied to handheld gamma detection probe systems, are also the focus of current preclinical research that is actively looking at developing small platform, portable perioperative and intraoperative patient and ex vivo surgical specimen imaging devices which possess similar capabilities for detecting

high-energy gamma photon-emitting/positron-emitting radionuclides [76]. However, such small platform, portable perioperative and intraoperative patient and ex vivo surgical specimen imaging devices have not yet been fully realized or made commercially available for use in the setting of clinical medicine.

25.4.3 Beta plus Decay (i.e., Positron) Detection

The detector component of a beta plus detection probe generally consists of a semiconductor ionization detector or an organic ("plastic") scintillator detector but for which an inorganic scintillator detector can also be utilized [6, 45, 52, 108, 115–127]. As previously mentioned, whereas high-energy 511 keV gamma photons can travel many, many centimeters within biological tissues, positrons travels only very short distances (i.e., approximately 1–2 mm) within biological tissues before they are annihilated. This difference in the distances traveled by positrons as opposed to resultant high-energy 511 keV gamma photons within biologic tissues contributes to both the advantages and disadvantages of direct detection of positrons by a handheld beta plus detection probe. Thus, handheld beta plus detection probes can be small in physical size and light in weight secondary to the fact that whereas gamma photon detection of high-energy 511 keV gamma photons relies heavily on the thickness of side and back shielding and the length of collimation, beta plus decay detection of positrons does not require any significant degree of side and back shielding or collimation. However, whereas gamma photon detection of high-energy 511 keV gamma photons is less effected by the distance from the source of 511 keV gamma emissions to the proximity of the head of the handheld gamma detection probe, beta plus decay detection requires close apposition of the head of the handheld beta plus detection probe to the source of the positrons emitted from the biologic tissue. As a result, if the head of the handheld beta plus detection probe is not in direct contact with the biologic tissue emitting positrons, or if the source of the positrons emitted from the biologic tissue is located several millimeters below of the surface of that biologic tissue, the handheld beta plus detection probe will be unable to detect such ^{18}F-FDG-avid tissues. Along similar lines, the simple placement of a sterile disposable barrier sheath over the handheld beta plus detection probe significantly reduces the overall sensitivity for the detection of ^{18}F-FDG-avid tissues by such a device.

25.5 Clinical Applications of Real-Time ^{18}F-FDG-Directed Surgery and Real-Time ^{18}F-FDG-Directed Interventional Procedures (Tables 25.1 and 25.2)

The principal motivation behind the use of ^{18}F-FDG for providing for real-time cancer detection and guidance within the operating room has been multifactorial, including exploring its applicability for real-time intraoperative staging, surgical planning and execution, and determination of completeness of surgical resection [6]. The clinical application of ^{18}F-FDG-directed surgery was first described in 1999 by Desai et al. from the Ohio State University (Columbus, Ohio, USA) for colorectal cancer [6, 26, 27]. In this first clinical description of ^{18}F-FDG-directed surgery, a total of 15 colorectal cancer patients received an intravenous injection of 4.0–5.7 mCi (148–211 MBq) of ^{18}F-FDG at a time of 58–110 min prior to intraoperative evaluation with a commercially available gamma detection probe. Fourteen of these 15 patients had undergone a prior preoperative diagnostic ^{18}F-FDG PET scan. A single or multiple tumor foci were identified with the gamma detection probe as ^{18}F-FDG-avid tissue in 14 of the 15 patients receiving an intravenous injection of ^{18}F-FDG on the day of surgery. Likewise, a single or multiple tumor foci were correctly identified with the gamma detection probe as ^{18}F-FDG-avid tissue in 13 of 14 patients undergoing a prior preoperative diagnostic ^{18}F-FDG PET scan, correctly correlating to the sites of hypermetabolic activity seen on the prior preoperative diagnostic ^{18}F-FDG PET imaging.

Table 25.1 All reported published series for real-time ^{18}F-FDG-directed surgery

Primary author	Reference(s)	Year(s)	Location(s)	Number of patients	Known malignancies in patients evaluated	^{18}F-FDG dose	Injection-to-operation start time Injection-to-probing time Injection-to-postoperative specimen imaging time	Probe type(s)	Detection threshold criteria method (DTCM) and findings for ^{18}F-FDG-avid lesions with probe(s)
Desai	[26, 27]	1999, 2000	Columbus, OH, USA	15	Colorectal	Range, 4.0–5.7 mCi (Range, 148–211 MBq)	IOST: 40–100 min IPT: 58–110 min IPOSIT: ND	GDP	DTCM for GDP: three-sigma criteria Reported three-sigma criteria identified ^{18}F-FDG-avid lesions in 14 of 15 patients
Zervos	[28]	2001	Columbus, OH, USA	10	Colorectal	Range, 5–10 mCi (Range, 185–370 MBq)	IOST: NS IPT: NS IPOSIT: ND	GDP BDP	DTCM for GDP: three-sigma criteria and T/B ratio Reported three-sigma criteria identified ^{18}F-FDG-avid lesions in 5 of 5 patients for GDP Reported mean (range) T/B ratios 1.53:1 (1.25:1–1.78:1) for ^{18}F-FDG-avid lesions for GDP DTCM for BDP: T/B ratio Reported mean (range) T/B ratios 1.64:1 (1.11:1–2.17:1) for ^{18}F-FDG-avid lesions for BDP
Essner	[29, 30]	2001	Santa Monica, CA, USA	8	Colorectal, melanoma	Range, 7–10 mCi (Range, 259–370 MBq)	IOST: “up to 3 h” IPT: “up to 4 h later” IPOSIT: ND	GDP	DTCM for GDP: T/B ratio $\geq$ 1.5:1 Reported T/B ratio $\geq$ 1.5:1 identified 11 of 17 ^{18}F-FDG-avid lesions Reported range T/B ratios in vivo: 1.16:1–7.92:1 for ^{18}F-FDG-avid lesions

Yen	[32]	2004	Taoyuan, Taiwan	2	Cervical	2 and 5 mCi (74 and 185 MBq)	IOST: NS IPT: NS IPOSIT: ND	GDP BDP	DTCM for GDP: T/B ratio DTCM for BDP: T/B ratio Reported T/B ratios: 1.78:1 and 1.53:1 for ^{18}F-FDG-avid lesions, but not specified for which probe type
Franc	[36]	2005	San Francisco, CA, USA	5	Melanoma	Mean, 14.6 (±3.2) mCi (Mean, 540 (±118) MBq)	IOST: 178–240 min IPT: NS IPOSIT: ND	HEGDP BDP	DTCM for GDP: T/B ratio DTCM for BDP: T/B ratio Reported identified 3 of 5 ^{18}F-FDG-avid lesions, but not specified for which probe type Reported range T/B ratios: 1.2:1–10:1 for ^{18}F-FDG-avid lesions, but not specified for which probe type
Kraeber-Bodéré	[37, 41]	2005, 2007	Nantes, France	10	Thyroid	Mean, 7.2 (4.5–14.2) mCi (Mean, 265 (165–526) MBq)	IOST: ≈30 min IPT: NS	GDP	DTCM for GDP: T/B ratio Reported mean(range) T/B ratios in vivo: 1.40:1 (0.76:1–2.59:1) for ^{18}F-FDG-avid lesions Reported mean(range) T/B ratios ex vivo: 2.44:1 (1.18:1–7.89:1) for ^{18}F-FDG-avid lesions
Gulec	[38, 43]	2006	Santa Monica, CA, USA	40	Breast, colorectal, lymphoma, melanoma, seminoma, thyroid	Range, 7–10 mCi (Range, 259–370 MBq)	IOST: 1–4 h IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: T/B ratio ≥ 1.5:1 Reported T/B ratio ≥ 1.5:1 identified 40 of 40 ^{18}F-FDG-avid lesions (cumulatively from in situ and ex vivo T/B ratios Reported mean (range) T/B ratios in situ: 1.9:1 (1.4:1–2.5:1) for ^{18}F-FDG-avid lesions Reported mean (range) T/B ratios ex vivo: 2.1:1 (1.5:1–3.3:1) for ^{18}F-FDG-avid lesions

(continued)

Table 25.1 (continued)

Primary author	Reference(s)	Year(s)	Location(s)	Number of patients	Known malignancies in patients evaluated	^{18}F-FDG dose	Injection-to-operation start time Injection-to-probing time Injection-to-postoperative specimen imaging time	Probe type(s)	Detection threshold criteria method (DTCM) and findings for ^{18}F-FDG-avid lesions with probe(s)
Nwogu	[40]	2006	Buffalo, NY, USA	10	Lung	10 mCi (370 MBq)	IOST: "within 4 h" IPT: NS IPOSIT: ND	GDP	DTCM for GDP: T/B ratio Reported T/B ratio ≥ 3.0:1 ex vivo for primary tumor site in 10 of 10 cases and T/B ratio ≥ 2.0:1 ex vivo for lymph nodes in 8 of 10 cases
Gulec	[42, 43]	2007	Goshen, IN, USA	25	Adrenocortical, breast, carcinoma of unknown primary, colorectal, gastric, GIST, head and neck, lung, lymphoma, melanoma, ovarian, thyroid	Range, 5–15 mCi (Range, 185–555 MBq)	IOST: 2–6 h IPT: NS IPOSIT: ND	HEGDP	DTCM for HE GDP: T/B ratio ≥ 1.5:1 Reported T/B ratio ≥ 1.5:1 identified 24 of 25 ^{18}F-FDG-avid lesions Reported range T/B ratios: 1.5 to 3.8 for ^{18}F-FDG-avid lesions
Povoski	[6, 44, 46–51, 53, 54, 56, 67, 71, 73–76]	2007–2015	Columbus, OH, USA	157	Breast, cervical, colorectal, eccrine, endometrial, head and neck, lung lymphoma, melanoma, ovarian, plasmacytoma, sarcoma, thyroid, urothelial	Mean, 15.1 (4.6–26.1) mCi (Mean, 559 (170–966) MBq)	IOST: NS IPT: mean (range): 286 (176–532) minutes IPOSIT: mean (range): 389 (86–741) minutes on diagnostic scanner and mean (range): 458 (272–656) minutes on micro scanner	GDP HEGDP	DTCM for GDP: Three-sigma criteria and T/B ratio DTCM for HEGDP: three-sigma criteria and T/B ratio Reported ^{18}F-FDG-avid lesions identified in 156 of 157 patients, but the details for identification of the ^{18}F-FDG-avid lesions was not specifically delineated according to probe type or DTCM

Piert	[45, 52]	2007	Munich, Germany	17	Breast, colorectal, esophageal, gastric, gastroesophageal, melanoma, thyroid	Range, 1–3 mCi (Range, 36.6–110.6 MBq)	IOST: NS IPT: mean (range): 184 (19–365) minutes IPOSIT: ND	HEGDP BDP	DTCM for HEGDP: NS DTCM for BDP: T/B ratio ≥ 1.5:1 Reported T/B ratio ≥ 1.5:1 identified 16 of 17 ^{18}F-FDG-avid lesions for BDP Reported mean (range) T/B ratios ex vivo: 6.6:1 (1.3:1–17.2:1) for ^{18}F-FDG-avid lesions for BDP
Van Baardwijk	[55]	2008	Maastricht, The Netherlands	5	Lung	Median, 0.97 (0.92–1.24) mCi (Median, 36 (34–46) MBq)	IOST: ND IPT: ND IPOSIT: median (range): 180 (150–300) minutes	ND	ND (no intraoperative probing performed, and only postoperative specimen imaging performed) The ^{18}F-FDG-avid lesion(s) was identified in 5 of 5 cases on postoperative specimen imaging
Gollub	[57]	2009	New York, NY, USA	5	Colorectal, colonic polyps	Range, 15–20 mCi (Range, 555–740 MBq)	IOST: ND IPT: ND IPOSIT: mean (range): 195 (169–223) minutes	ND	ND (no intraoperative probing performed, and only postoperative specimen imaging performed) The ^{18}F-FDG-avid lesion(s) was identified in 5 of 5 cases on postoperative specimen imaging
Molina[a]	[58]	2009	Miami, Florida, USA	10	Breast, gastric, lymphoma, melanoma	Range, 10–12 mCi (Range, 370–444 MBq)	IOST: 3–4 h IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: NS Reported that HEGDP correctly identified 14 ^{18}F-FDG-avid lesions

(continued)

Table 25.1 (continued)

Primary author	Reference(s)	Year(s)	Location(s)	Number of patients	Known malignancies in patients evaluated	^{18}F-FDG dose	Injection-to-operation start time Injection-to-probing time Injection-to-postoperative specimen imaging time	Probe type(s)	Detection threshold criteria method (DTCM) and findings for ^{18}F-FDG-avid lesions with probe(s)
De Jong	[61]	2010	Groningen, Germany	3	Testicular	0.14 mCi/kg body weight (5 MBq/kg body weight)	IOST: 3 h IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: T/B ratio ≥ 1.5:1 Reported T/B ratio ≥ 1.5:1 identified in 4 ^{18}F-FDG-avid lesions, with T/B ratio ≥ 5.0:1 in all cases
Lee	[62]	2010	San Francisco, CA, USA	2	Melanoma	11.4 and 16.6 mCi (422 and 614 MBq)	IOST: NS IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: T/B ratio Reported T/B ratios: 4.4:1 and 2.2:1 for ^{18}F-FDG-avid lesions
García	[64]	2011	Barcelona, Spain	7	Colorectal, ovarian, thyroid	Mean, 10.0 (9.5–10.5) mCi (Mean, 370 (352–389) MBq)	IOST: 3–5 h IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: T/B ratio Reported T/B ratio ≥ 1.5:1 identified 14 of 16 ^{18}F-FDG-avid lesions Reported range T/B ratios: 1.5–2.5 for ^{18}F-FDG-avid lesions

Kim	[65]	2011	Dauegu, Seoul, and Jeju, Korea	12	Thyroid	Mean, 9.8 (6.1–15.4) mCi (Mean, 363 (227–570) MBq)	IOST: mean (range): 228 (134–395) minutes IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: T/B ratio >1.3:1 Reported mean (range) T/B ratios ex vivo for confirmed tumor sites: 1.51:1 (1.17:1–4.03:1) for ^{18}F-FDG-avid lesions Reported mean (range) T/B ratios ex vivo for confirmed benign sites: 1.14 (1.01:1–1.48:1) for ^{18}F-FDG-avid lesions
Francis	[68]	2012	Little Rock, AK, USA Hershey, PA, USA	4	Thyroid	NS	IOST: "at least 2 h" IPT: NS IPOSIT: ND	GDP HEGDP	DTCM for GDP: NS DTCM for HEGDP: NS No specific probe localization data was reported
Vos	[70]	2012	Amsterdam, The Netherlands	9	Breast, colorectal, esophageal, skin, lymphoma, melanoma, thyroid	0.095 mCi/kg body weight (3.5 MBq/kg body weight)	IOST: ≈4 h IPT: NS IPOSIT: ND	HEGDP	DTCM for HEGDP: NS Reported that HEGDP identified ^{18}F-FDG-avid lesions in 9 of 9 patients

All reported series in Table 25.1 represent those reported series with greater than one reported patient in their series, and for which any additional references representing single case reports and/or review papers from the same institution were also added to any reported series with greater than one reported patient in their series

For all reported series in Table 25.1 in which there were multiple reports from the same institution and in which it appeared that the study patients were derived from the same overall patient population, these reported series were combined under the name of the predominant primary author from that institution, and the total "number of patients" from that institution was estimated as based upon the available data within all the reports from that same institution which appeared to be derived from the same overall patient population

Abbreviations: *BDP* beta plus detection probe, *DTCM* detection threshold criteria method, *^{18}F-FDG* fluorine-18 fluorodeoxyglucose, *GDP* gamma detection probe, *GIST* gastrointestinal stromal tumor, *HEGDP* high-energy gamma detection probe ("PET probe"), *IOST* injection-to-operation start time, *IPOSI* injection-to-postoperative specimen imaging time, *IPT* injection-to-probing time, *MBq* megabecquerels, *mCi* millicuries, *NS* not clearly specified in the reported series, *ND* not done in the reported series, *SUVmax* maximum standardized uptake value, *T/B ratio* target-to-background ratio for detection of ^{18}F-FDG-avid lesion

[a]Personal communication from Manuel A. Molina (Lakeland Regional Cancer Center, Lakeland, Florida, USA, manmolina@hotmail.com, February 25, 2015) confirms a total of 14 ^{18}F-FDG-avid lesions identified from among a total of 10 patients undergoing ^{18}F-FDG-directed surgery (and with 2 patients having no ^{18}F-FDG-avid lesion identifiable with the HEGDP at the time of ^{18}F-FDG-directed surgery)

Table 25.2 All reported published series for real-time ^{18}F-FDG-directed diagnostic and interventional procedures

Primary author	Reference(s)	Year(s)	Location(s)	Interventional procedure	Number of patients	Known malignancies in patients evaluated	^{18}F-FDG dose	Injection-to-scan time Injection-to-procedure time	^{18}F-FDG-avid lesion SUVmax
Klaeser	[79, 80]	2009, 2010	Bern, Switzerland	Biopsies	28	Breast, cervical, lung, lymphoma, melanoma, ovarian, sarcoma	Range, 0.08–0.19 mCi/kg body weight (Range, 3–7 MBq/kg body weight)	IST: 60–180 min IPT: NS	NS
Tatli	[81]	2011	Boston, MA, USA	Biopsies	12	Breast, colorectal, lung, melanoma, ovarian, lymphoma	Mean, 20.6 (16.6–23.9) mCi (Mean, 762 (614–884) MBq)	IST: 61–78 min IPT: ≈120 min	3.9–19.1
Shyn	[82, 83, 89, 90]	2011–2014	Boston, MA, USA	Biopsies and ablations	12	Breast, colorectal, esophageal, lung, ovarian, sarcoma	Mean, 14.7 (10.4–16.8) mCi (Mean, 544 (385–622) MBq)	IST: 78–130 min IPT: ≈120 min	1.5–23.1
Ryan	[85, 86]	2013	New York, NY, USA	Ablations	23	Colorectal, endometrial, head and neck, hepatocellular, lung, melanoma, pancreas, sarcoma	Pre-ablation dose: median, 4.2 (3. 6–4.4) mCi (median, 155 (133–163) MBq) Post-ablation assessment dose: median 8.4 (7.6–8.8) mCi (median 310 (281–326) MBq)	IST: 40–143 min (for pre-ablation scan) IPT: NS IST: NS (for post-ablation assessment scan)	NS
Cerci[a]	[87, 91]	2013, 2014	Curitiba, Parcanà, Brazil	Biopsies	126	Breast, carcinoma of unknown primary, cervical, colorectal, gastric, head and neck, lung, lymphoma, melanoma, other, prostate,	Range, 8–12 mCi (Range, 296–444 MBq)	IST: ≈60 –90 min IPT: NS	3.5–27.6

Aparici	[88, 92, 93]	2013, 2014	San Francisco, CA, USA	Biopsies	4	Esophageal, lymphoma, prostate	5 mCi (185 MBq)	IST: 60 min IPT: NS	NS
Cornelis	[95]	2014	New York, NY, USA	Biopsies	105	Breast, colorectal, endometrial, esophageal, gastric, germ cell, head and neck, lung, lymphoma, melanoma, pancreas, plasmacytoma, prostate, renal cell, sarcoma, skin, small bowel, thyroid, vulva	Mean, 6.9 (3.9–13.2) mCi (Mean, 255 (144–288) MBq)	IST: 35–183 min IPT: NS	1.9–44.4

All reported series in Table 25.2 represent those reported series with greater than one reported patient in their series, and for which any additional references representing single case reports and/or review papers from the same institution were also added to any reported series with greater than one reported patient in their series

For all reported series in Table 25.2 in which there were multiple reports from the same institution and in which it appeared that the study patients were derived from the same overall patient population, these reported series were combined under the name of the predominant primary author from that institution, and the total "number of patients" from that institution was estimated as based upon the available data within all the reports from that same institution which appeared to be derived from the same overall patient population

Abbreviations: *^{18}F-FDG* fluorine-18 fluorodeoxyglucose, *IPT* injection-to-procedure time, *IST* injection-to-scan time, *MBq* megabecquerels, *mCi* millicuries, *NS* not clearly specified in the reported series, *SUVmax* maximum standardized uptake value

[a]Cerci et al. [91] mention "update of our group's result" as "217 PET/CT-guided biopsies performed," but without formal presentation of accompanying data

Subsequent to the first report of ^{18}F-FDG-directed surgery in 1999 [6, 26, 27], multiple groups of investigators from across the globe have collectively investigated the utility of real-time ^{18}F-FDG-directed surgery and real-time ^{18}F-FDG-directed diagnostic and therapeutic interventional procedures in regard to a wide range of solid malignancies, including colorectal cancer, gastric cancer, gastroesophageal cancer, pancreatic cancer, melanoma, lymphoma, breast cancer, ovarian cancer, endometrial cancer, cervical cancer, vulvar cancer, testicular cancer, prostate cancer, head and neck malignancies (squamous cell cancer of the oral cavity, oropharynx, hypopharynx, and laryngeal regions, iodine-negative recurrent papillary thyroid cancer, and recurrent medullary thyroid cancer), lung cancer, squamous cell cancer of the skin, GIST (gastrointestinal stromal tumor tumors), sarcoma, adrenocortical carcinoma, and carcinoma of unknown primary [6, 28–95]. Table 25.1 summarizes all reported real-time ^{18}F-FDG-directed surgery series in the literature [6, 26–76]. Table 25.2 summarizes all reported real-time ^{18}F-FDG-directed diagnostic and therapeutic interventional procedure series in the literature [6, 77–95]. It is worth noting a substantial portion of the clinical investigations into the use of ^{18}F-FDG for real-time detection and guidance during cancer surgery for a variety of solid malignancies have been conducted at the Ohio State University (Columbus, Ohio, USA) [6, 26–28, 44, 46–51, 53, 54, 56, 59, 67, 71–76].

Our own experience with utilizing ^{18}F-FDG for real-time cancer detection and guidance within the operating room at the Ohio State University (Columbus, Ohio, USA) [6, 26–28, 44, 46–51, 53, 54, 56, 59, 67, 71–76] has strengthened our long-standing contention regarding the importance of implementing a multimodal imaging and detection approach to ^{18}F-FDG-directed surgery [50, 67, 74, 76]. Since 2005, the general structure of this multimodal approach has incorporated various components, including (1) same-day preoperative patient diagnostic whole-body PET/CT imaging, (2) intraoperative gamma detection probe assessment, (3) specimen imaging of surgically resected specimens with both a clinical PET/CT unit and a micro PET/CT unit, (4) radioactivity counting of selected portion of surgically resected specimens by an automatic gamma well counter, and (5) same-day postoperative patient diagnostic limited field-of-view PET/CT imaging [67].

On the day of the anticipated ^{18}F-FDG-directed surgery procedure, patients fasted for a minimum of 6 h before undergoing the same-day preoperative diagnostic whole-body ^{18}F-FDG PET/CT scan [67, 74]. Each patient received a same-day, single-dose, preoperative, intravenous injection of ^{18}F-FDG, consisting of an averaged recommended dose in the range of approximately 15 mCi (555 MBq). The ^{18}F-FDG dosing at the Ohio State University (Columbus, Ohio, USA) was based upon the standard-of-care practice guidelines set in the USA by the Society of Nuclear Medicine, the American College of Radiology, and the Society for Pediatric Radiology for diagnostic ^{18}F-FDG PET/CT image acquisition (i.e., 10–20 mCi (370–740 MBq) of ^{18}F-FDG in adults) [128, 129]. The same-day, single-dose, preoperative, intravenous dose of ^{18}F-FDG was generally administered approximately 75 min prior to the planned time of the same-day preoperative diagnostic whole-body ^{18}F-FDG PET/CT scan, which was performed within the time frame recognized by the standard-of-care practice guidelines set in the USA by the Society of Nuclear Medicine, the American College of Radiology, and the Society for Pediatric Radiology for diagnostic ^{18}F-FDG PET/CT image acquisition [128, 129]. The same-day preoperative diagnostic whole-body ^{18}F-FDG PET/CT scan usually consisted of 6–8 field-of-view PET bed positions and with 2 min of PET imaging for each field-of-view PET bed position. Patients then proceeded to the operating room for their anticipated surgical procedure and completed standard postoperative recovery in the postanesthesia care unit. The same-day postoperative diagnostic limited field-of-view ^{18}F-FDG PET/CT scan was generally restricted to those field-of-view PET bed positions encompassing the immediate area of the surgical field (usually consisting of 1–3 field-of-view PET bed positions, in order to limit overall patient radiation

exposure for the CT portion of the PET/CT, and with 10 min of PET imaging for each field-of-view PET bed position).

Our multimodal imaging and detection approach to ^{18}F-FDG-directed surgery at the Ohio State University (Columbus, Ohio, USA) [50, 67, 74, 76] demonstrated technical and logistical feasibility for coordination of services by the surgeon, nuclear medicine physician, and pathologist in a same-day fashion. It allowed for (1) real-time intraoperative staging of the extent of disease; (2) real-time intraoperative surgical planning and execution of the necessary and most appropriate operation, determination of the extent of surgical resection, and determination of the completeness of surgical resection; (3) real-time pathologic evaluation of intact surgical resected specimens for the confirmation of completeness of surgical resection and for surgical margin assessment; and (4) real-time pathologic evaluation of diagnostically biopsied tissues for confirmation of correctness of tissue diagnosis.

25.6 Timing Issues Related to ^{18}F-FDG-Directed Surgery: Impact of Length of Time from Injection of ^{18}F-FDG to the Performance of Intraoperative Gamma Detection Probing

Numerous investigators have evaluated the concept of delayed phase and dual-time-point diagnostic ^{18}F-FDG PET imaging [74] in which a portion of the diagnostic ^{18}F-FDG PET imaging sequence is extended temporally out further than is generally recommended by the standard-of-care practice guidelines for diagnostic ^{18}F-FDG PET/CT image acquisition [128, 129]. Remarkably, several of these groups of investigators have performed delayed phase diagnostic ^{18}F-FDG PET imaging out to ultra-extended injection-to-scan acquisition time intervals ranging to 6–9 h after the initial ^{18}F-FDG injection dose is administered [31, 74, 130–134].

In contrast to the innumerous work done on extended injection-to-scan acquisition time intervals for diagnostic ^{18}F-FDG PET imaging, there has been very little data or discussion in the literature regarding the equivalent scenario of extended injection-to-probing time intervals as it pertains to gamma detection probing of patients intravenously injected with ^{18}F-FDG [31, 38, 42, 43, 74]. Therefore, it is reasonable to say that the optimal length of time from the injection of ^{18}F-FDG to the performance of intraoperative gamma detection probing has yet to be determined.

In 2004, Higashi et al. [31, 74] examined the question of "appropriate timing" for "postinjection" gamma detection probing using phantom studies and a limited series of 3 patients with "superficially located malignant lesions." For the phantom studies, they used 5 liter plastic barrels filled with saline containing varying-dose "background" ^{18}F-FDG as the "body trunk" phantom, 0.2 liter plastic bottles filled with saline containing varying-dose ^{18}F-FDG as the "kidney" phantom, and 2 fixed-dose ^{18}F-FDG sources to simulate "superficially located tumor nodules." For the 3 patients with "superficially located malignant lesions," they performed "preoperative" gamma detection probing at the skin surface at 1, 3, 5, 6, and/or 7 h after receiving an intravenous injection of 2–10 mCi (74–370 MBq) of ^{18}F-FDG (and for which no intraoperative gamma detection probing was undertaken). In their limited patient data set, they showed that the tumor-to-background ratios of ^{18}F-FDG by gamma detection probing at the skin surface remained relatively stable at the measured time intervals and remained relatively stable up to the 7-h postinjection time interval. However, they were concerned that the overall lower ^{18}F-FDG count rates encountered at time intervals of 6–7 h postinjection of ^{18}F-FDG, secondary to the normal physical decay pattern of ^{18}F-FDG, "would be problematic" when applied to a clinical application of intraoperative gamma detection probing. Therefore, they concluded that the clinical application of intraoperative gamma detection probing was "more suitable" at 1–3 h postinjection of ^{18}F-FDG as compared to 6–7 h postinjection of ^{18}F-FDG.

In 2006 and 2007, Gulec et al. [38, 42, 43, 74] reported on two consecutive series of patients, including 40 patients undergoing intraoperative

gamma detection probing after receiving an intravenous injection of 7–10 mCi (259–370 MBq) of ^{18}F-FDG [38] and 25 patients undergoing intraoperative gamma detection probing after receiving an intravenous injection of 5–15 mCi (185–555 MBq) of ^{18}F-FDG [42]. In both series, Gulec et al. [38, 42, 43] reported observing a nonsignificant trend toward an increased tumor-to-background ratio of ^{18}F-FDG as the duration of time from the ^{18}F-FDG injection to performing intraoperative gamma detection probing increased, with satisfactory count rates and lesion detection capabilities up to 6 h of time after injection of ^{18}F-FDG. Therefore, regarding intraoperative gamma detection probing during ^{18}F-FDG-directed surgery, they concluded that longer injection-to-probing time intervals "accentuated" the tumor-to-background ratio of ^{18}F-FDG and resulted in "better lesion detection" [38, 42]. However, they also stated that "more delayed intervals between FDG injection and imaging might compromise image quality as a result of lower count rates" [42].

Most recently, in 2014, our group at the Ohio State University (Columbus, Ohio, USA) [74] examined the question of extended injection-to-scan acquisition time intervals in a retrospective data analysis of a subset of patients undergoing ^{18}F-FDG-directed surgery. This data analysis specifically looked at preoperative ^{18}F-FDG PET/CT imaging and postoperative ^{18}F-FDG PET/CT imaging of 32 individual ^{18}F-FDG-avid lesions (from among a total of 7 patients) which were not surgically manipulated or altered during ^{18}F-FDG-directed surgery, and, for which, all of these 32 individual ^{18}F-FDG-avid lesions were visualized on both same-day preoperative ^{18}F-FDG PET/CT imaging and same-day postoperative ^{18}F-FDG PET/CT imaging. In this retrospective data analysis, both ^{18}F-FDG-avid lesions and their corresponding background tissues were assessed on same-day preoperative and postoperative ^{18}F-FDG PET/CT scans. This data analysis demonstrated several important time-dependent observations. First, ^{18}F-FDG PET/CT imaging performed at extended injection-to-scan acquisition times of up to a mean time of 530 min (i.e., approximately five half-lives for ^{18}F-FDG) was able to maintain a designation of good/adequate diagnostic image quality deemed necessary for clinical interpretation. Second, the mean ^{18}F-FDG-avid lesion SUV_{max} value increased significantly from preoperative to postoperative ^{18}F-FDG PET/CT imaging (mean ^{18}F-FDG-avid lesion SUV_{max} value; 7.7 preoperative to 11.3 postoperative; $P < 0.001$). Third, mean background SUV_{max} value decreased significantly from preoperative to postoperative ^{18}F-FDG PET/CT imaging (mean background SUV_{max} value; 2.3 preoperative to 2.1 postoperative; $P = 0.017$). Fourth, the mean lesion-to-background SUV_{max} ratio increased significantly from preoperative to postoperative ^{18}F-FDG PET/CT imaging (mean lesion-to-background SUV_{max} ratio; 3.7 preoperative to 5.8 postoperative; $P < 0.001$).

The far-reaching implications of these collective time-dependent observations [74] appear highly influential for guiding future direction in ^{18}F-FDG-directed procedural and surgical applications, as well as ^{18}F-FDG PET/CT oncologic imaging. First and foremost, these time-dependent observations justify the more widespread and integrated, real-time use of diagnostic ^{18}F-FDG PET/CT imaging in conjunction with ^{18}F-FDG-directed interventional radiology diagnostic biopsy procedures and therapeutic ablation procedures, as well as with ^{18}F-FDG-directed surgical procedures. These sorts of integrated, real-time utilities for diagnostic ^{18}F-FDG PET/CT imaging would facilitate periprocedural verification of appropriate tissue targeting during ^{18}F-FDG-directed interventional radiology diagnostic biopsy procedures and therapeutic ablation procedures and for perioperative verification of appropriate tissue targeting and completeness of resection during ^{18}F-FDG-directed surgical procedures. Secondly but still importantly, these time-dependent observations could have far-reaching impact on potentially reshaping future thinking regarding what represents the "most optimal" injection-to-scan acquisition time interval for all routine diagnostic ^{18}F-FDG PET/CT oncologic imaging.

25.7 Inherent Challenge of In Situ Detection of ^{18}F-FDG with a Gamma Photon Detection Device When Encountering a Low Target-to-Background Ratio of ^{18}F-FDG and the Impact of Threshold Detection Criteria Methodology on the Determination of Gamma Detection Probe Positivity for Intraoperative In Situ Identification of ^{18}F-FDG-Avid Tissue Sites during ^{18}F-FDG-Directed Surgery

A significant challenge faced during attempted intraoperative in situ identification of ^{18}F-FDG-avid tissue sites with a gamma photon detection device during ^{18}F-FDG-directed surgery is a scenario in which a low target-to-background ratio (i.e., low tumor-to-background ratio) of high-energy 511 keV gamma photon emissions is encountered within the surgical field [6, 31, 38, 42, 43, 45, 52, 73, 75, 115–126]. As previously discussed, a low target-to-background ratio of high-energy 511 keV gamma photon emissions can results from a multitude of factors, including the marginal ^{18}F-FDG uptake by certain tumor-bearing tissues, the distribution and degree of intrinsic physiologic background ^{18}F-FDG activity within adjacent surrounding tissues which do not represent tumor-bearing tissues, and innumerable factors related to the technical specifications of the specific gamma photon detection device used for generating the counts per second measurements [75]. In this regard, some investigators have suggested that a minimum in situ target-to-background ratio of 1.5-to-1 for ^{18}F-FDG is necessary for allowing the surgeon to comfortably differentiate tumor-bearing tissues from normal tissue during ^{18}F-FDG-directed surgery [38, 42, 43, 73, 75]. However, a target-to-background ratio of 1.5-to-1 simply represents an arbitrary and fixed ratio determination.

Our personal experience with ^{18}F-FDG-directed surgery at the Ohio State University (Columbus, Ohio, USA) [6, 26–28, 44, 46–51, 53, 54, 56, 59, 67, 71–76] clearly indicates that the observed in situ target-to-background ratio of ^{18}F-FDG-avid tissue sites is frequently less than 1.5-to-1 and is highly dependent upon the specific gamma photon detection device utilized. Resultantly, when intraoperative detection of in situ ^{18}F-FDG-avid tissue sites relies solely on a fixed target-to-background ratio (i.e., a ratiometric threshold method) as the threshold for probe positivity, the success of intraoperative detection can be limited and provide unsatisfactory results to the surgeon [73, 75]. Therefore, our own group has long contended that improved intraoperative in situ identification of ^{18}F-FDG-avid tissue sites during ^{18}F-FDG-directed surgery can be better accomplished by the use of the three-sigma statistical threshold criteria method for determination of gamma detection probe positivity. The three-sigma statistical threshold criteria defines any given tissue as being probe positive when the count rate in that tissue exceeds three standard deviations above the mean count rate detected within normal adjacent tissue.

In order to comparatively assess the efficacy of the 1.5-to-1 ratiometric threshold criteria method and the three-sigma statistical threshold criteria method for determination of gamma detection probe positivity for intraoperative in situ detection of ^{18}F-FDG-avid tissue sites during ^{18}F-FDG-directed surgery, we evaluated a total of 401 intraoperative gamma detection probe measurement sets of in situ counts per second measurements collected from our prospective, pilot study database and performed our analysis in a manner that was completely independent of the specific type of gamma detection probe system that was used for determination of the counts per second measurements [75]. Our data analysis demonstrated that the three-sigma statistical threshold criteria method was significantly better than the 1.5-to-1 ratiometric threshold criteria method (P <0.001) for determining gamma detection probe positivity for intraoperative in situ detection of ^{18}F-FDG-avid tissue sites during

^{18}F-FDG-directed surgery. Likewise, the three-sigma statistical threshold criteria method was able to detect true positive results at target-to-background counts ratios that were much lower than could be detected by a ratiometric threshold criteria method that set the target-to-background count ratio cutoff at 1.5-to-1. Thus, if a surgeon utilized a gamma detection probe system with high count rate sensitivity, it was theoretically feasible that target-to-background count ratios as low as 1.1-to-1 could be identified as in situ probe positive when applying the three-sigma statistical threshold criteria method. Therefore, use of the three-sigma statistical threshold criteria for determination of gamma detection probe positivity for intraoperative in situ detection of ^{18}F-FDG-avid tissue sites during ^{18}F-FDG-directed surgery proved instrumental for overcoming the commonly encountered scenario of a low target-to-background ratio (i.e., low tumor-to-background ratio).

25.8 Occupational Radiation Exposure to Intraoperative and Perioperative Personnel from ^{18}F-FDG Radioguided Surgical Procedures

Occupational radiation exposure incurred by intraoperative and perioperative personnel participating in surgical cases has been previously evaluated by several groups of investigators [37, 41, 44–46, 52, 54, 55, 57, 60, 61, 64, 67, 135–137]. These investigators have reported data based upon several different study-design scenarios, including utilizing simulated surgical cases [46, 135, 136], surgical cases in which the patient was injected with ^{18}F-FDG but in which actual ^{18}F-FDG-directed surgery with intraoperative utilization of radiation detection probes was not undertaken for assisting in the surgical procedure [55, 57, 137], and actual ^{18}F-FDG-directed surgery cases [37, 41, 44, 45, 52, 54, 60, 61, 64, 67].

The most comprehensive evaluation of occupational radiation exposure to intraoperative and perioperative personnel participating in ^{18}F-FDG-directed surgery cases was published in 2008 by our group at the Ohio State University (Columbus, Ohio, USA) [54, 67]. In this comprehensive study, 10 actual ^{18}F-FDG-directed surgery cases were evaluated. A mean dose of 18.9 mCi (699 MBq) of ^{18}F-FDG was intravenously injected at a mean time of 142 min prior to surgery. The resultant mean deep dose equivalent per case for the surgeon, anesthetist, scrub technologist, postoperative nurse, circulating nurse, and preoperative nurse was 164, 119, 92, 63, 54, and 48 μSv, respectively.

The results of this comprehensive evaluation were used to determine the estimated number of ^{18}F-FDG-directed surgery cases per year and the estimated number of hours of exposure per year that could be theoretically incurred by the surgeon, anesthetist, scrub technologist, postoperative nurse, circulating nurse, and preoperative nurse in both the USA and internationally [54, 67]. Based upon the established annual occupational exposure limit for adults within the USA of a total effective dose equivalent of 50,000 μSv (as defined by the US Nuclear Regulatory Commission) [54, 138], the estimated number of ^{18}F-FDG-directed surgery cases per year and the estimated number of hours of exposure per year that could be theoretically incurred by the surgeon, anesthetist, scrub technologist, postoperative nurse, circulating nurse, and preoperative nurse were 305 cases and 820 h, 420 cases and 1020 h, 543 cases and 2083 h, 794 cases and 1471 h, 926 cases and 2941 h, and 1042 cases and 602 h, respectively [54]. In contrast to the annual occupational exposure limit for adults within the USA, the annual occupational exposure limit for the adult international community outside the USA (as defined by the International Commission on Radiological Protection (ICRP)) is more stringent and complex, with the annual occupational exposure limit for adults to be a total effective dose equivalent of 20,000 μSv per year, averaged over a 5-year period (100,000 μSv in 5 years), with further provision that the total effective dose equivalent should not exceed 50,000 μSv in any single year [54, 139, 140]. Based upon the established annual occupational exposure limit for the adult international

community outside the USA defined by the International Commission on Radiological Protection (ICRP), the estimated number of ^{18}F-FDG-directed surgery cases per year and the estimated number of hours of exposure per year that could be theoretically incurred by the surgeon, anesthetist, scrub technologist, postoperative nurse, circulating nurse, and preoperative nurse were 122 cases and 328 h, 168 cases and 408 h, 217 cases and 833 h, 317 cases and 588 h, 370 cases and 1176 h, and 417 cases and 241 h, respectively [54]. The data outlined in this comprehensive evaluation [54, 67] clearly illustrated that the absorbed radiation dose received by both intraoperative and perioperative personnel involved in ^{18}F-FDG-directed surgery cases was relatively low per case and allows for all such personnel to participate in multiple cases and still remain well below regulatory standards set for occupational radiation exposure limits.

25.9 Concluding Remarks

The use of positron-emitting and high-energy gamma photon-emitting radiopharmaceuticals, like ^{18}F-FDG, for real-time cancer detection and surgical guidance within the operating room and for real-time guidance of diagnostic and therapeutic interventional procedures within the interventional radiology suite, has great clinical potential. When a multimodal imaging and detection approach to ^{18}F-FDG-directed surgery is utilized, thus coordinating of services provided by the surgeon, nuclear medicine physician, and pathologist, this integrated approach has the potential for allowing (1) real-time intraoperative staging of the extent of disease; (2) real-time intraoperative surgical planning and execution of the necessary and most appropriate operation, determination of the extent of surgical resection, and determination of the completeness of surgical resection; (3) real-time pathologic evaluation of intact surgical resected specimens for the confirmation of completeness of surgical resection and for surgical margin assessment; (4) real-time pathologic evaluation of diagnostically biopsied tissues for confirmation of correctness of tissue diagnosis; and (5) real-time guidance of diagnostic and therapeutic interventional procedures within the interventional radiology suite. However, major hurdles still exist for maximizing the clinical potential of these technologies. The greatest challenges that remain involve the need for the development of more technically optimized handheld radiation detection probes for positron-emitting and high-energy gamma photon-emitting radiopharmaceuticals, like ^{18}F-FDG, as well as the need for the development of portable positron and high-energy gamma photon imaging devices that can be fully integrated into the operative/perioperative arena for real-time intraoperative/perioperative patient and specimen imaging. If these hurdles can be overcome, the use of positron-emitting and high-energy gamma photon-emitting radiopharmaceuticals for real-time cancer detection and surgical guidance within the operating room and for real-time guidance of diagnostic and therapeutic interventional procedures within the interventional radiology suite can become more fully realized and potentially impactful upon the long-term outcome for cancer patients.

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